UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/075,322	02/14/2002	David T. Curiel	D6392	8688

7590 11/05/2003

Benjamin Aaron Adler
ADLER & ASSOCIATES
8011 Candle Lane
Houston, TX 77071

EXAMINER	
NGUYEN, QUANG	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 11/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/075,322	CURIEL ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-12 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-12 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 8/15/02 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to comply* .

DETAILED ACTION

Claims 1-12 are pending in the present application.

Applicant's election without traverse of Group III (claims 1-12) in Paper dated 09/02/03 is acknowledged. Applicants further elected vascular endothelial growth factor type I receptor promoter as a species of a tissue-specific promoter.

Claims 1-12 are examined on the merits herein.

Claim Objections

Claims 2 and 8 are objected to because they recite non-elected subject matters (e.g., targeting component is incorporated into the fiber protein of the adenoviral vector by genetic mutation, and targeting ligand incorporated into a capsid protein of the adenoviral vector by genetic mutation). Appropriate correction is required.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth below and on the attached Notice to Comply with Requirements for Patent Applications containing nucleotide sequence and/or amino acid sequence disclosures.

Specifically, the specification discloses the amino acid sequence "SIGYPLP" that has not been assigned with a SEQ ID NO. (see page 15, line 10). Failure to comply

with the sequence rule will be deemed as non-responsive in the reply of this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

With respect to the elected invention, the claims are drawn to a method of gene delivery by adenoviral vector comprising the step of contacting target cells with an adenoviral vector comprising a targeting component that targets said vector to specific target cells and a tissue-specific promoter that drives the expression of a transgene

carried by said vector in said target cells, wherein said adenoviral vector has increased targeting specificity to said targeting cells and results in reduced transgene expression in non-target cells, and wherein the targeting component of said adenoviral vector is a bi-specific molecule that binds to the knob protein of said adenoviral vector and a molecule expressed on said target cells.

The specification teaches by exemplification the preparation of a recombinant AdfltLuc whose luciferase gene expression is operably linked to the endothelial specific promoter flt-1, and the pulmonary endothelial targeting conjugate Fab-9B9 (a conjugate of the Fab fragment of an anti-Ad5 knob antibody 1D6.14 to the mAb 9B9 specific for angiotensin converting enzyme). Applicants further demonstrate that a conjugate-based approach to target pulmonary endothelium *in vivo* via binding to angiotensin converting enzyme in combination with the usage of flt-1 promoter results in a high degree of activity in and specificity for endothelial cells (see example 5 and Figs. 3-5).

When read in light of the specification, the sole purpose for a method of gene delivery by adenoviral vector as claimed is to obtain therapeutic effects *in vivo*, particularly for treating pulmonary vascular diseases (see Summary of the Invention on pages 6-9). The instant disclosure does not teach any other uses for the gene delivery method as claimed. It should be noted that enablement requires the specification to teach how to make and **use** the claimed invention.

(1) The breadth of the claims.

With respect to the elected invention, the instant broad claims encompass a method of gene delivery by adenoviral vector comprising the step of contacting target

cells by any route of administration with an adenoviral vector comprising a targeting component which is a bi-specific molecule that binds to the knob protein of the adenoviral vector and a molecule expressed on the target cells, and a tissue-specific promoter that drives the expression of any transgene to attain therapeutic results contemplated by Applicants.

(2) The state and the unpredictability of the art.

The nature of the instant claims falls within the realm of *in vivo* gene therapy. The specification is not enabled for the instant invention because at about the effective filing date of the present application, gene therapy was an immature and highly unpredictable art, particularly for the attainment of any therapeutic effects. This is supported by numerous reviews in the art. For example, Dang et al. (Clin. Cancer Res. 5:471-474, 1999) state "This workshop reviewed some recent advances in gene delivery, gene expression, immune manipulation, and the development of molecular targets and stressed that all of these fields will need further advancement to make gene therapy a reality" (page 471, col. 1, last sentence of first paragraph). At about the effective filing date of the present application (2/14/2001), Romano et al. (Stem Cells 18:19-39, 2000) note that "The potential therapeutic applications of gene transfer technology are enormous. However, the effectiveness of gene therapy programs is still questioned...., despite the latest significant achievements reported in vector design, it is not possible to predict to what extent gene therapeutic interventions will be effective in patients, and in what time frame" (see the abstract). It has been recognized that there are several factors limiting an effective gene therapy, and these include sub-optimal

vectors, a lack of a stable *in vivo* transgene expression, and an efficient gene delivery to target tissues or cells. With respect to gene therapy specific for pulmonary diseases, West et al. (Chest 119:613-617, 2001) also note several important barriers that will need to be overcome, including the host inflammatory response, promoter down-regulation, tissue-specific targeting and physical barriers to gene delivery in the airway. West et al. further state "Demonstration of successful gene delivery and transcription has been quite variable in human trials. In general, the level of expression of transgene appears to be quite low. In summary, although there is a great promise for gene therapy in the lung, significant challenges remain in translating this technology to successful human therapy" (see abstract). More recently, Griesenbach et al. (Gene therapy 9:1344-1350, 2002) noted that cystic fibrosis gene transfer efficiency was still low, and most likely insufficient to achieve clinical effect (see abstract).

Thus, it is clear that the attainment of any therapeutic effect through the gene therapy approach was highly unpredictable at the effective filing date of the present application.

(3) The amount of direction or guidance presented.

The instant specification is not enabled for the presently claimed invention. Apart from the exemplification showing the qualitative assessment of luciferase activity or carcinoembryonic antigen gene expression being enhanced in the pulmonary endothelium via a systemic delivery of the AdfltLuc-1D6.14/9B9 complex or AdfltCEA-1D6.14/9B9 complex, respectively in rats, the present disclosure fails to provide any evidence indicating that any therapeutic effect has been achieved *in vivo*, particularly in

light of the unpredictable attainment of therapeutic effects via gene therapy known in the art. The specification fails to provide any relevant *in vivo* example (part of guidance) demonstrating that a therapeutic effect has been obtained, particularly for a pulmonary vascular disease, using the modified adenoviral vector system disclosed in the present application. Despite an enhanced detection of luciferase activity and expression of carcinoembryonic antigen in pulmonary endothelium, it is noted that significant expression levels of luciferase were still detected in liver, spleen, muscle, testis, brain and heart tissues of the treated rats (see Figs. 3-5). Furthermore, Sato et al. (Biochem. Biophys. Res. Commun. 244:455-462, 1998) have noted that the use of any tissue-specific promoters for specific cancer gene therapy has been limited because the expression level of these promoters is generally low and may not be sufficient for effective gene therapy (page 455, col. 2, last sentence of first paragraph). Therefore, given the lack of sufficient guidance provided by the instant specification for a skilled artisan on how to overcome factors known to limit the effectiveness of gene therapy, it would have required undue experimentation for a skilled artisan to make and use the method as claimed.

Accordingly, due to the lack of sufficient guidance and examples provided by the instant specification regarding to the issues set forth above, the unpredictable nature of the gene therapy art, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and **use** the method as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1 and its dependent claims, it is not clear what is encompassed by the term "increased gene delivery". Increased gene delivery with respect to what? Clarification is requested because the metes and bounds of the claims are not clearly determined.

Similarly in claim 7 and its dependent claims, it is not clear what is encompassed by the term "increased targeting specificity". Increased targeting specificity with respect to what? Clarification is requested because the metes and bounds of the claims are not clearly determined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States

only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Sosnowski et al. (WO 98/40508).

With respect to the elected invention, the claims are drawn to an adenoviral vector that mediates increased gene delivery *in vivo* comprising: a targeting component that targets said vector to specific target cells; and a tissue-specific promoter that drives the expression of a transgene carried by said vector in said target cells, and wherein said targeting component is a bi-specific molecule that binds to the knob protein of said adenoviral vector and a molecule expressed on said target cells.

Sosnowski et al. disclose a tropism-modified adenoviral vector system that specifically target cells (page 4, lines 17-25) comprising: (i) an antibody or fragment thereof that binds an adenoviral capsid protein (e.g., an adenoviral knob protein, line 27 on page 8 continues to line 3 of page 9), (ii) a targeting ligand that bind to the specifically target cells (including a ligand is an antibody or a fragment thereof, and that the ligand is conjugated to an antibody or fragment thereof that binds an adenoviral knob protein, line 27 on page 8 continues to line 3 of page 9), and (iii) an adenovirus containing a nucleic acid molecule that encodes a therapeutic gene product under the control of a promoter, including a tissue-specific promoter such as the endothelial-specific VEGF-receptor promoter (elected species, page 75, line 17 continues to line 19 of page 76). Sosnowski et al. further teach the utilization of bi-specific antibodies (see the section on Bi-specific Antibodies, pages 28-33, particularly page 30, lines 14-17) that recognizes an Ad knob protein (e.g., 1D6.14 antibody or its Fab fragment known for

its high affinity binding to recombinant Ad5 knob and its ability to neutralize Ad5 infection of HeLa cells) as well as the target cell-specific receptor to ablate endogenous adenoviral tropism. Sosnowski et al. also teach that any antibody that recognizes a molecule internalized following binding, including but not limited to antibodies to molecules on endothelial cells such as antibodies to FGF receptors, VEGF receptors, E- and P-selectins and others (see pages 43-48).

Accordingly, the adenoviral vector system of Sosnowski et al. meets every limitation of the instant claims, and therefore Sosnowski et al. anticipate the instant claims.

Claims 1-2 are rejected under 35 U.S.C. 102(e) as being anticipated by Sosnowski et al. (U.S. Patent 6,613,563).

Sosnowski et al. disclose a tropism-modified adenoviral vector system that specifically target cells (col. 3, lines 25-38) comprising: (i) an antibody or fragment thereof that binds an adenoviral capsid protein (e.g., an adenoviral knob protein, col. 6, lines 9-18), (ii) a targeting ligand that bind to the specifically target cells (including a ligand is an antibody or a fragment thereof, and that the ligand is conjugated to an antibody or fragment thereof that binds an adenoviral knob protein, col. 6, lines 9-18), and (iii) an adenovirus containing a nucleic acid molecule that encodes a therapeutic gene product under the control of a promoter, including a tissue-specific promoter such as the endothelial-specific VEGF-receptor promoter (elected species, col. 46, line 62 continues to line 43 of col. 47). Sosnowski et al. further teach the utilization of bi-

specific antibodies (see the section on Bi-specific Antibodies, cols. 18-21) that recognizes an Ad knob protein (e.g., 1D6.14 antibody or its Fab fragment known for its high affinity binding to recombinant Ad5 knob and its ability to neutralize Ad5 infection of HeLa cells) as well as the target cell-specific receptor to ablate endogenous adenoviral tropism. Sosnowski et al. also teach that any antibody that recognizes a molecule expressed on the surface of target cells can be utilized as long as the antibody is internalized following binding, including but not limited to antibodies to molecules on endothelial cells such as antibodies to FGF receptors, VEGF receptors, E- and P-selectins and others (see cols. 27-31).

Accordingly, the adenoviral vector system of Sosnowski et al. meets every limitation of the instant claims, and therefore Sosnowski et al. anticipate the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sosnowski et al. (WO 98/40508) in view of Muzykantov et al. (Am. J. Physiol. 270: L704-L713, 1996; IDS).

Sosnowski et al. disclose a tropism-modified adenoviral vector system that specifically target cells (page 4, lines 17-25) comprising: (i) an antibody or fragment thereof that binds an adenoviral capsid protein (e.g., an adenoviral knob protein, line 27 on page 8 continues to line 3 of page 9), (ii) a targeting ligand that bind to the specifically target cells (including a ligand is an antibody or a fragment thereof, and that the ligand is conjugated to an antibody or fragment thereof that binds an adenoviral knob protein, line 27 on page 8 continues to line 3 of page 9), and (iii) an adenovirus containing a nucleic acid molecule that encodes a therapeutic gene product under the control of a promoter, including a tissue-specific promoter such as the endothelial-specific VEGF-receptor promoter (elected species, page 75, line 17 continues to line 19 of page 76). Sosnowski et al. further teach the utilization of bi-specific antibodies (see the section on Bi-specific Antibodies, pages 28-33, particularly page 30, lines 14-17) that recognizes an Ad knob protein (e.g., 1D6.14 antibody or its Fab fragment known for its high affinity binding to recombinant Ad5 knob and its ability to neutralize Ad5 infection of HeLa cells) as well as the target cell-specific receptor to ablate endogenous

adenoviral tropism. Sosnowski et al. also teach that any antibody that recognizes a molecule internalized following binding, including but not limited to antibodies to molecules on endothelial cells such as antibodies to FGF receptors, VEGF receptors, E- and P-selectins and others (see pages 43-48).

Sosnowski et al. do not teach specifically the utilization of a bi-specific antibody conjugate linking a Fab fragment of an anti-Ad5 knob antibody with an anti-angiotensin converting enzyme antibody, more specifically a bi-specific antibody conjugate linking 1D6.14 and 9B9 antibody, in their tropism-modified adenoviral vector system.

However, at the effective filing date of the present application Muzykantov et al. already disclose that the Mab 9B9 to angiotensin converting enzyme is a safe and specific carrier for drug targeting to the pulmonary endothelium, and that it is internalized by endothelial cells both *in vitro* and *in vivo* without significant intracellular degradation (see abstract).

Accordingly, it would have been obvious for an ordinary skilled artisan in the art to modify the tropism-modified adenoviral vector system of Sosnowski et al. by utilizing a bi-specific antibody conjugate linking a Fab fragment of an anti-Ad5 knob antibody with an anti-angiotensin converting enzyme antibody, and more specifically the bi-specific antibody conjugate linking 1D6.14 and 9B9 antibody to target the modified adenoviral vector specifically to pulmonary endothelium in light of the teachings of Muzykantov.

One of ordinary skilled artisan would have been motivated to carry out the above modification because Muzykantov et al. already teach that Mab 9B9 is a safe and

specific carrier for drug targeting to the pulmonary endothelium and that the antibody is internalized by endothelial cells both *in vitro* and *in vivo* and that it is not significantly degraded intracellularly. Moreover, Sosnowski et al. clearly teach that any antibody that recognizes a molecule expressed on the surface of target cells can be utilized as long as the antibody is internalized following binding, including but not limited to antibodies to molecules on endothelial cells, and that 1D6.14 antibody or its Fab fragment is already known for its high affinity binding to recombinant Ad5 knob and its ability to neutralize Ad5 infection of HeLa cells.

One would have a reasonable expectation of success to carry out the presently claimed invention in light of the teachings of Sosnowski et al. and Muzykantov et al., coupled with a high level of skills of an ordinary skilled artisan in the art of making modified adenoviral vectors at the effective filing date of the present application.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Gerald Leffers, Jr., Ph.D., may be reached at (703) 305-6232, or SPE, Remy Yucel, Ph.D., at (703) 305-1998.

Quang Nguyen, Ph.D.

REMY YUCEL, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600